Selexipag

Uptravi®
Antithrombotic agent

FORMULATION

Selexipag (Uptravi®) is available in film-coated tablets for oral administration:

- Selexipag (Uptravi®) 200 mcg is a light yellow, round, unscored film-coated tablet with "2" debossed on one side. Each film-coated tablet contains 200 micrograms of selexipag.
- Selexipag (Uptravi®) 400 mcg is a red, round, unscored film-coated tablet with "4" debossed on one side. Each film-coated tablet contains 400 micrograms of selexipag.
- Selexipag (Uptravi®) 600 mcg is a light violet, round, unscored film-coated tablet with "6" debossed on one side. Each film-coated tablet contains 600 micrograms of selexipag.
- Selexipag (Uptravi®) 800 mcg is a green, round, unscored film-coated tablet with "8" debossed on one side. Each film-coated tablet contains 800 micrograms of selexipag.
- Selexipag (Uptravi®) 1000 mcg is an orange, round, unscored film-coated tablet with "10" debossed on one side. Each film-coated tablet contains 1000 micrograms of selexipag.
- Selexipag (Uptravi®) 1200 mcg is a dark violet, round, unscored film-coated tablet with "12" debossed on one side. Each film-coated tablet contains 1200 micrograms of selexipag.
- Selexipag (Uptravi®) 1400 mcg is a dark yellow, round, unscored film-coated tablet with "14" debossed on one side. Each film-coated tablet contains 1400 micrograms of selexipag.
- Selexipag (Uptravi®) 1600 mcg is a brown, round, unscored film-coated tablet with "16" debossed on one side. Each film-coated tablet contains 1600 micrograms of selexipag.

The excipients are:
Tablet contents: D-mannitol, corn starch, low substituted hydroxypropyl cellulose, hydroxypropyl cellulose and magnesium stearate.
Tablet coat: Hypromellose, propylene glycol, titanium dioxide, carnauba wax, iron oxide yellow (200 mcg, 600 mcg, 800 mcg, 1000 mcg, 1400 mcg and 1600 mcg tablets), iron oxide red (400 mcg, 1000 mcg, 1200 mcg and 1600 mcg tablets) and iron oxide black (600 mcg, 800 mcg, 1200 mcg and 1600 mcg tablets).

CLINICAL PHARMACOLOGY

Mechanism of action

The vasculo-protective effects of prostacyclin (PGI_2) are mediated by the prostacyclin receptor (IP receptor). Decreased expression of IP receptors and decreased synthesis of prostacyclin contribute to the pathophysiology of PAH.

Selexipag is an oral, selective, IP receptor agonist, and is structurally and pharmacologically distinct from prostacyclin and its analogs. Selexipag is hydrolyzed by carboxylesterases to yield its active metabolite, which is approximately 37-fold more potent than selexipag. Selexipag and the active metabolite are high affinity IP receptor agonists with a high selectivity for the IP receptor versus other prostanoid receptors (EP_1-EP_4, DP, FP and TP). Selectivity against EP_1, EP_3, FP and TP is important because these are well-described contractile receptors in gastro-intestinal tract and blood vessels. Selectivity against EP_2, EP_4 and DP_1 is important because these receptors mediate immune depressive effects.

Stimulation of the IP receptor by selexipag and the active metabolite leads to vasodilatory as well as anti-proliferative and anti-fibrotic effects. Selexipag improves hemodynamic variables and prevents cardiac

and pulmonary remodeling in a rat model of PAH. In these PAH rats, pulmonary and peripheral vasodilation in response to selexipag correlate, indicating that peripheral vasodilation reflects pulmonary pharmacodynamic efficacy. Selexipag does not cause IP receptor desensitization *in vitro* nor tachyphylaxis in a rat model.

PAH patients have variable degrees of IP receptor expression. Differences in maintenance dose of selexipag between individuals may be related to differences in IP receptor expression levels.

Pharmacodynamic effects

Effect on QT/QTc interval and cardiac electrophysiology
In a thorough QT study in healthy subjects, repeated doses of 800 and 1600 micrograms of selexipag (Uptravi®) tablets twice daily did not show an effect on cardiac repolarization (QT_c interval) or conduction (PR and QRS intervals) and had a mild accelerating effect on heart rate.

Clinical studies
Clinical studies/pharmacological properties
Clinical efficacy and safety of selexipag (Uptravi®) tablets

Efficacy of selexipag (Uptravi®) tablets in patients with PAH

The effect of selexipag (Uptravi®) tablets on progression of PAH was demonstrated in a multi-center, long-term (maximum duration of exposure approximately 4.2 years), double-blind, placebo-controlled, parallel group, event-driven Phase 3 study in 1156 patients with symptomatic [WHO FC I-IV] PAH. Patients were randomized to either placebo (N=582), or selexipag (Uptravi®) tablets (N=574) twice a day. The dose was increased in weekly intervals by increments of 200 micrograms given twice a day to determine the individualized maintenance dose (200-1600 micrograms twice a day).

The primary study endpoint was the time to first occurrence of a morbidity or mortality event up to end of treatment defined as a composite of death (all-causes); **or** hospitalization for PAH; **or** progression of PAH resulting in need for lung transplantation or balloon atrial septostomy; or initiation of parenteral prostanoid therapy or chronic oxygen therapy; **or** other disease progression events (patients in modified New York Heart Association [NYHA]/WHO FC II or III at baseline) confirmed by decrease in 6MWD from baseline (≥15%,) and worsening of NYHA/WHO FC **or** (patients in modified NYHA/WHO FC III or IV at baseline) confirmed by a decrease in 6MWD from baseline (≥15%,) and need for additional PAH specific therapy.

All events were confirmed by an independent adjudication committee, blinded to treatment allocation.

The mean age was 48.1 years (range 18-80 years of age) with the majority of subjects being Caucasian (65.0%) and female (79.8%). Approximately 1%, 46%, 53% and 1% of patients were in WHO FC I, II, III and IV, respectively, at baseline.

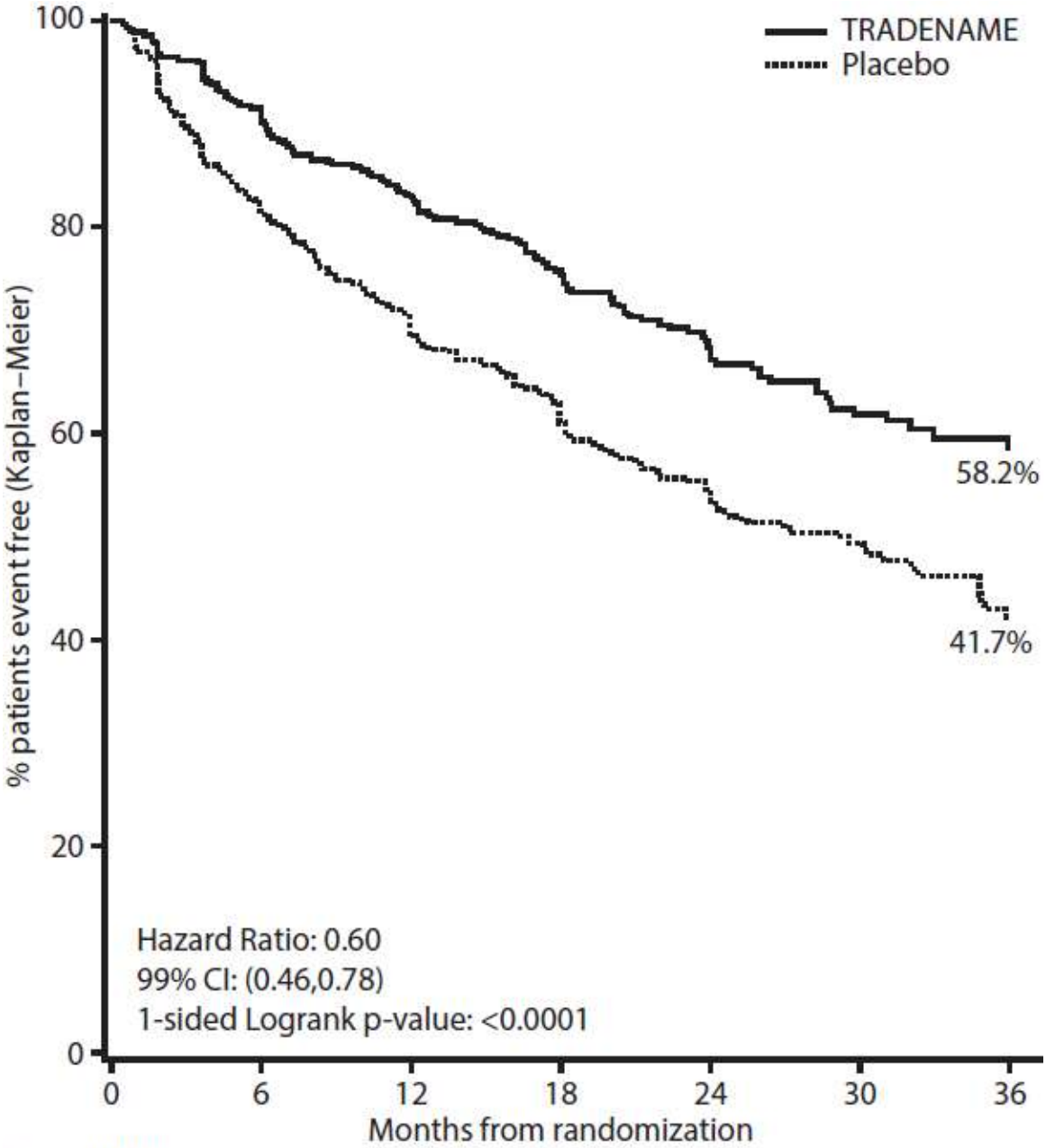
Idiopathic or heritable PAH was the most common etiology in the study population (58%) followed by PAH due to connective tissue disorders (29%), PAH associated with congenital heart disease with repaired shunts (10%), and PAH associated with other etiologies (drugs and toxins [2%] and HIV [1%]).

At baseline, the majority of enrolled patients (80%) were being treated with a stable dose of a specific therapy for PAH, either with an ERA (15%) or with a PDE-5 inhibitor (32%) or with both an ERA and a PDE-5 inhibitor (33%).

The overall median double-blind treatment duration was 63.7 weeks for the placebo group and 70.7 weeks for the group on selexipag (Uptravi®).

Treatment with selexipag (Uptravi®) tablets 200-1600 micrograms twice a day resulted in a 40% reduction (hazard ration [HR] 0.60; 99% CI: 0.46, 0.78; one-sided log-rank p-value < 0.0001) of the occurrence of morbidity or mortality events up to 7 days after last dose compared to placebo (Figure 1). The beneficial effect of selexipag (Uptravi®) was primarily attributable to a reduction in hospitalization for PAH and a reduction in other disease progression events. (Table 1).

Figure 1 Kaplan-Meier estimates of the first morbidity-mortality event in GRIPHON



TRADENAME patients:							
at risk	574	455	361	246	171	101	40
Placebo patients:							
at risk	582	433	347	220	149	88	28

Table 1 Type of first event as component of primary endpoint

	Selexipag (Uptravi®) N=574 n (%)	**Placebo N=582 n (%)**
Patients with a primary endpoint event	155 (27.0)	242 (41.6)
Component as first event		
Hospitalization for PAH	78 (13.6)	109 (18.7)
Disease progression	38 (6.6)	100 (17.2)
Death	28 (4.9)	18 (3.1)
i.v./s.c. prostanoid or chronic oxygen therapy	10 (1.7)	13 (2.2)
Need for lung transplantation or atrial septostomy	1 (0.2)	2 (0.3)

i.v. = intravenous; PAH = pulmonary arterial hypertension; s.c. = subcutaneous.

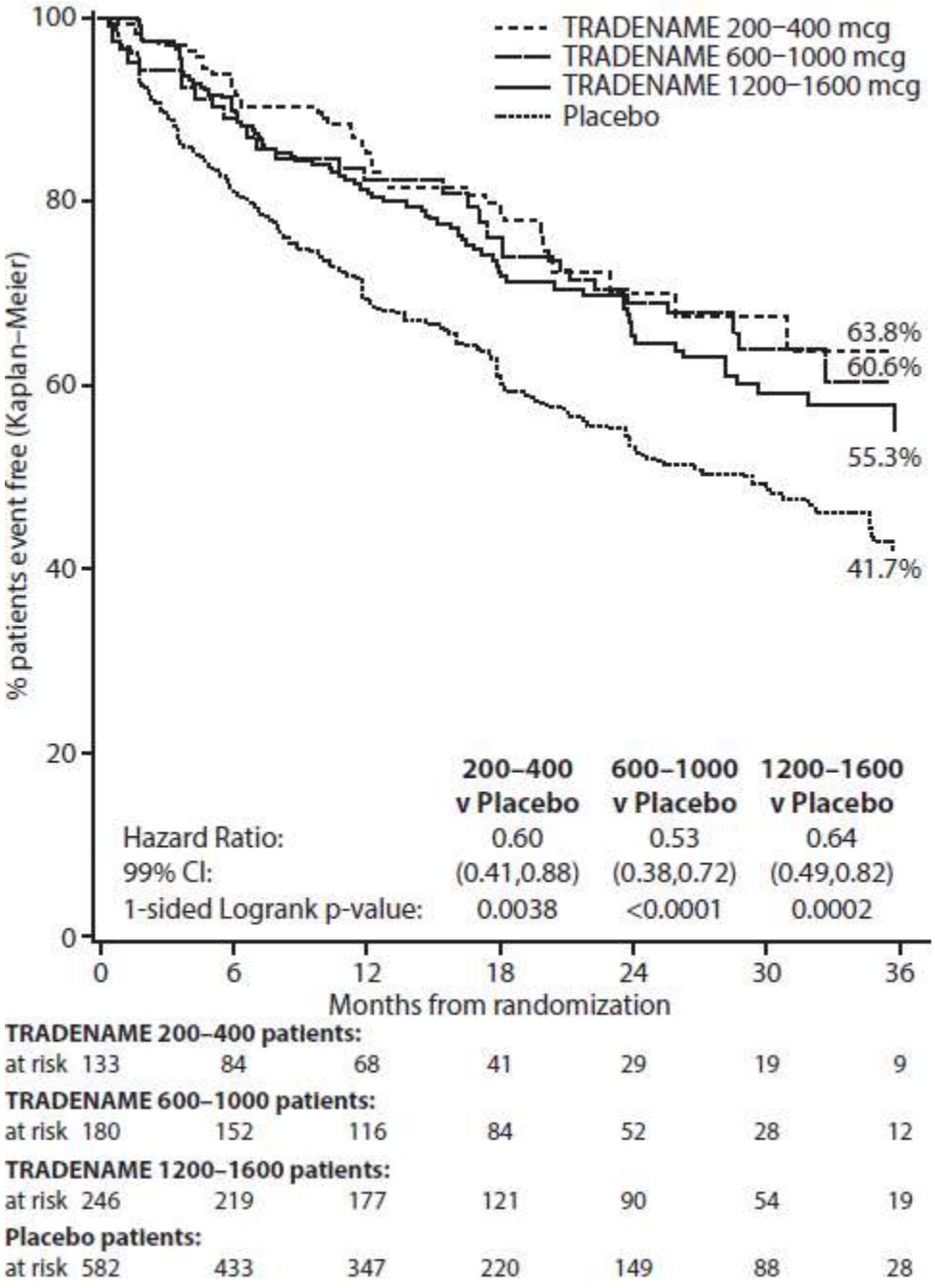
The observed effect of selexipag (Uptravi®) versus placebo on the primary endpoint was independent of the achieved individualized maintenance dose (IMD):

IMD 200–400 micrograms twice daily (23.2% of patients): HR 0.60 (95% CI: 0.41, 0.88, one-sided log-rank $p = 0.0038$).

IMD 600–1000 micrograms twice daily (31.4% of patients: HR 0.53 (95% CI: 0.38, 0.72, one-sided log-rank $p < 0.0001$).

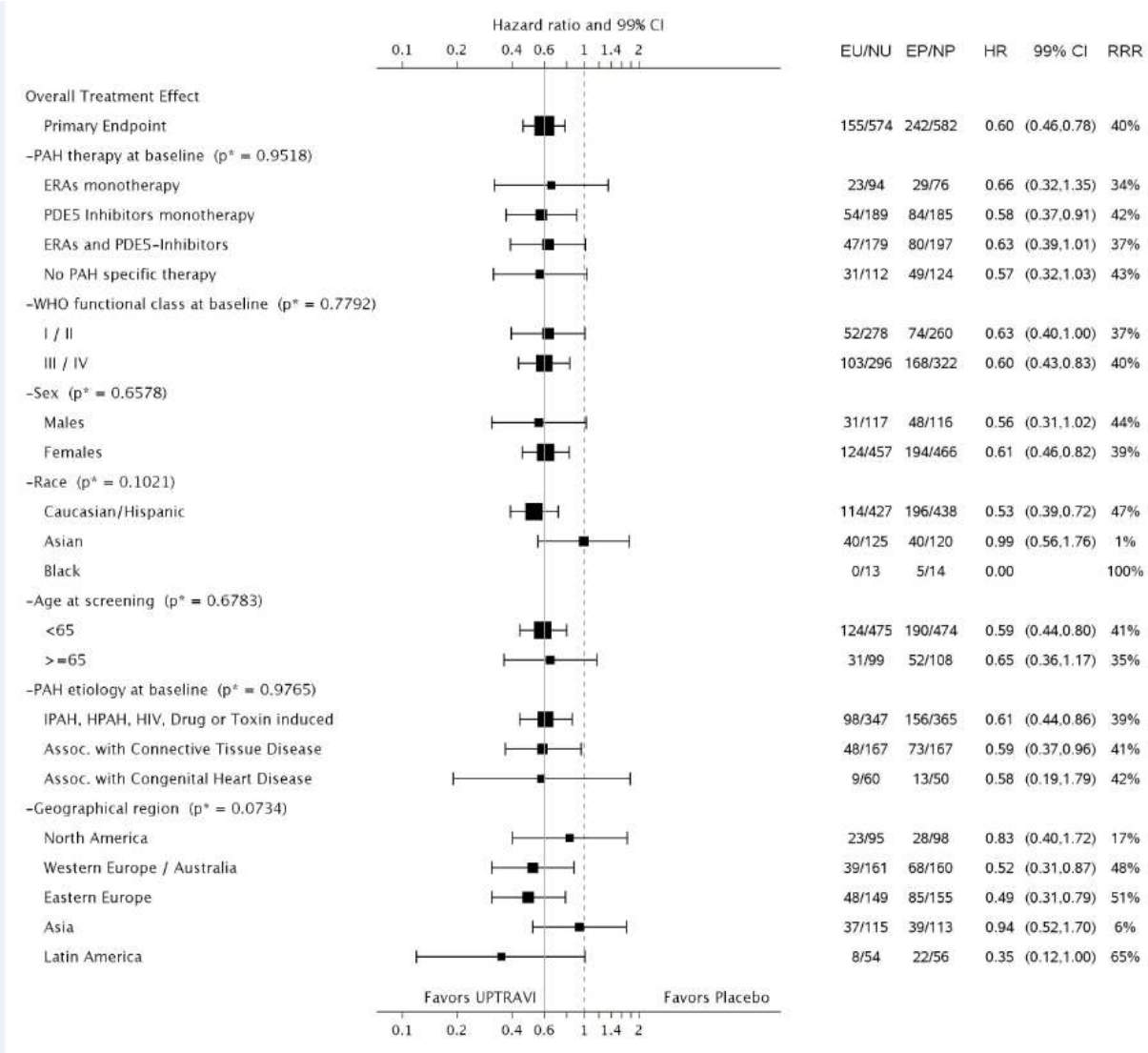
IMD 1200–1600 micrograms twice daily (42.9% of patients): HR 0.64 (95% CI: 0.49, 0.82, one-sided log-rank $p = 0.0002$).

Figure 2 Kaplan-Meier estimates of the first morbidity-mortality event in GRIPHON by individual maintenance dose group



Subgroup analyses were performed across subgroups of age, sex, race, etiology, geographical region, WHO FC, and by monotherapy or in combination with ERA, PDE-5 inhibitors or triple combination with both an ERA and a PDE-5 inhibitor (Figure 3).

Figure 3 Subgroup analyses of the primary endpoint in the GRIPHON study

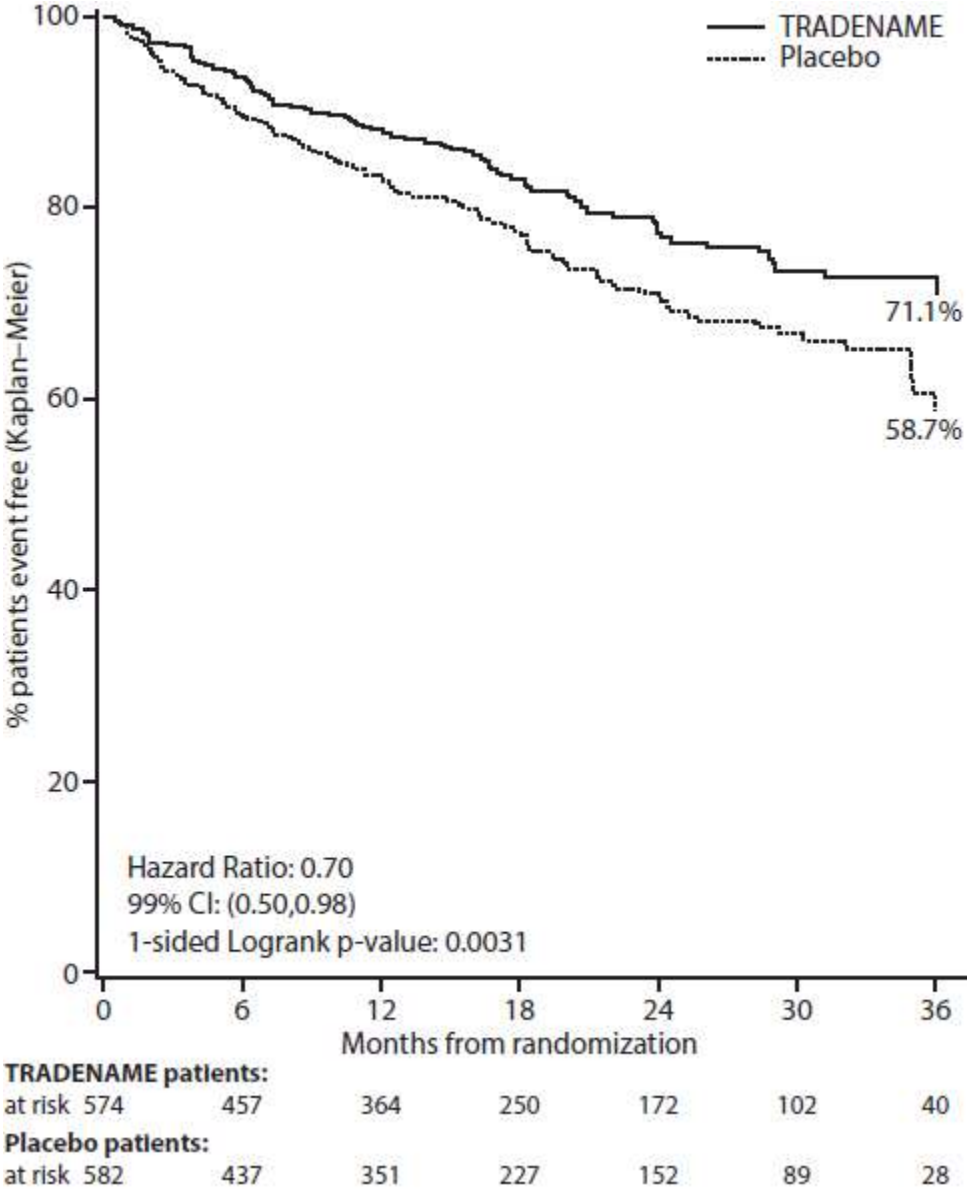


CI = confidence interval; EP = number of placebo patients with events; EU = number of selexipag (Uptravi®) patients with events; HR = hazard ratio; NP = number of patients randomized to placebo; NU = number of patients randomized to selexipag (Uptravi®); RRR = relative risk reduction.

The size of the square represents the number of patients in the subgroup.

Time to PAH-related death or hospitalization for PAH was assessed as a secondary endpoint. The risk of an event for this endpoint was reduced by 30% in patients receiving selexipag (Uptravi®) compared to placebo (HR 0.70, 99% CI: 0.50, 0.98; one-sided log-rank p = 0.0031) (Figure 4).

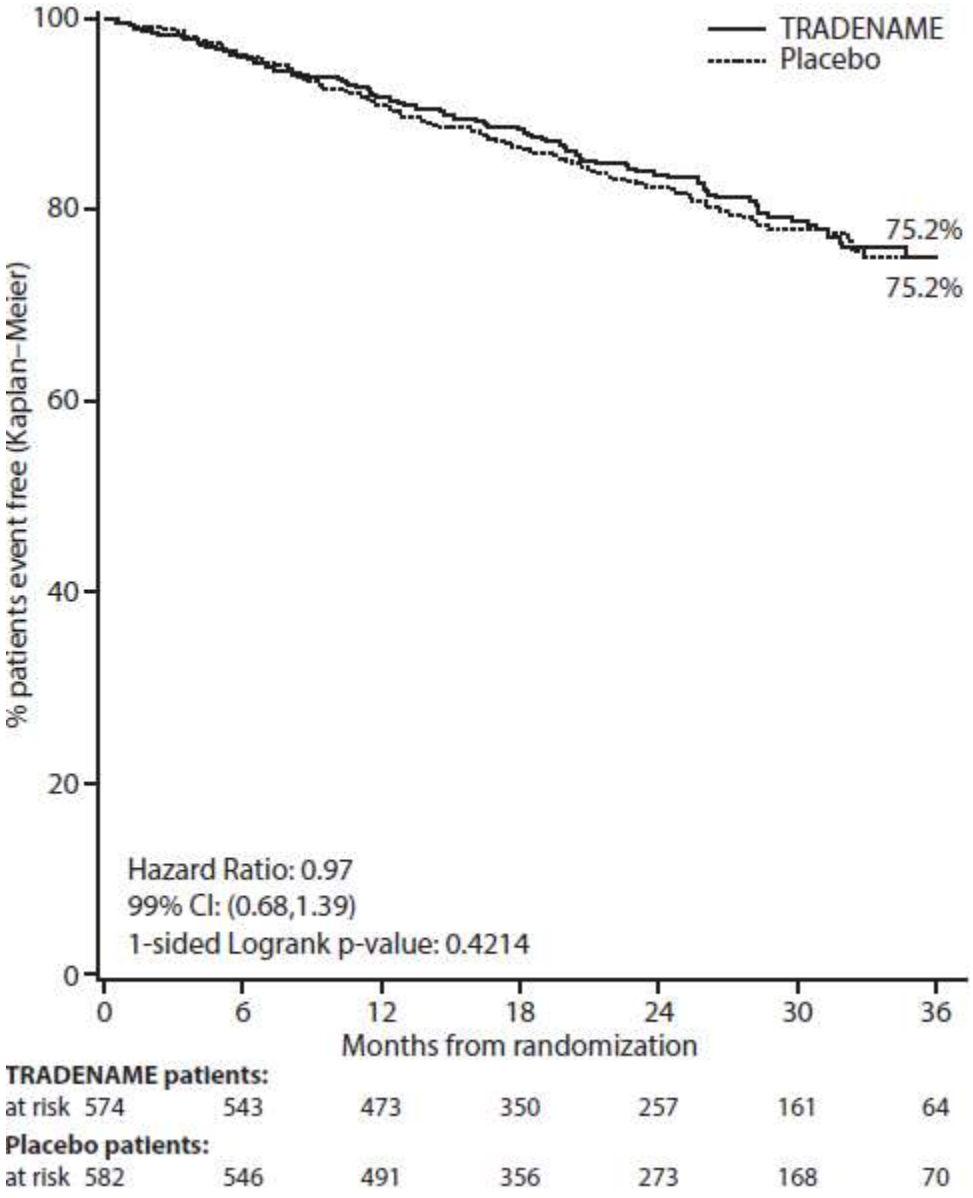
Figure 4 Kaplan-Meier estimates of the occurrence of death due to PAH or first hospitalization for PAH in GRIPHON



The number of patients who experienced as a first event, death due to PAH or hospitalization for PAH up to end of treatment was 102 (17.8%) in the selexipag (Uptravi®) group, and 137 (23.5%) in the placebo group. Death due to PAH as a component of the endpoint was observed in 16 (2.8%) patients on selexipag (Uptravi®) and 14 (2.4%) on placebo. Hospitalization for PAH was observed in 86 (15%) of patients on selexipag (Uptravi®) and 123 (21.1%) of patients on placebo. selexipag (Uptravi®) reduced the risk of hospitalization for PAH as first outcome event compared to placebo (HR 0.67, 99% CI: 0.46, 0.98); one-sided log-rank p = 0.04).

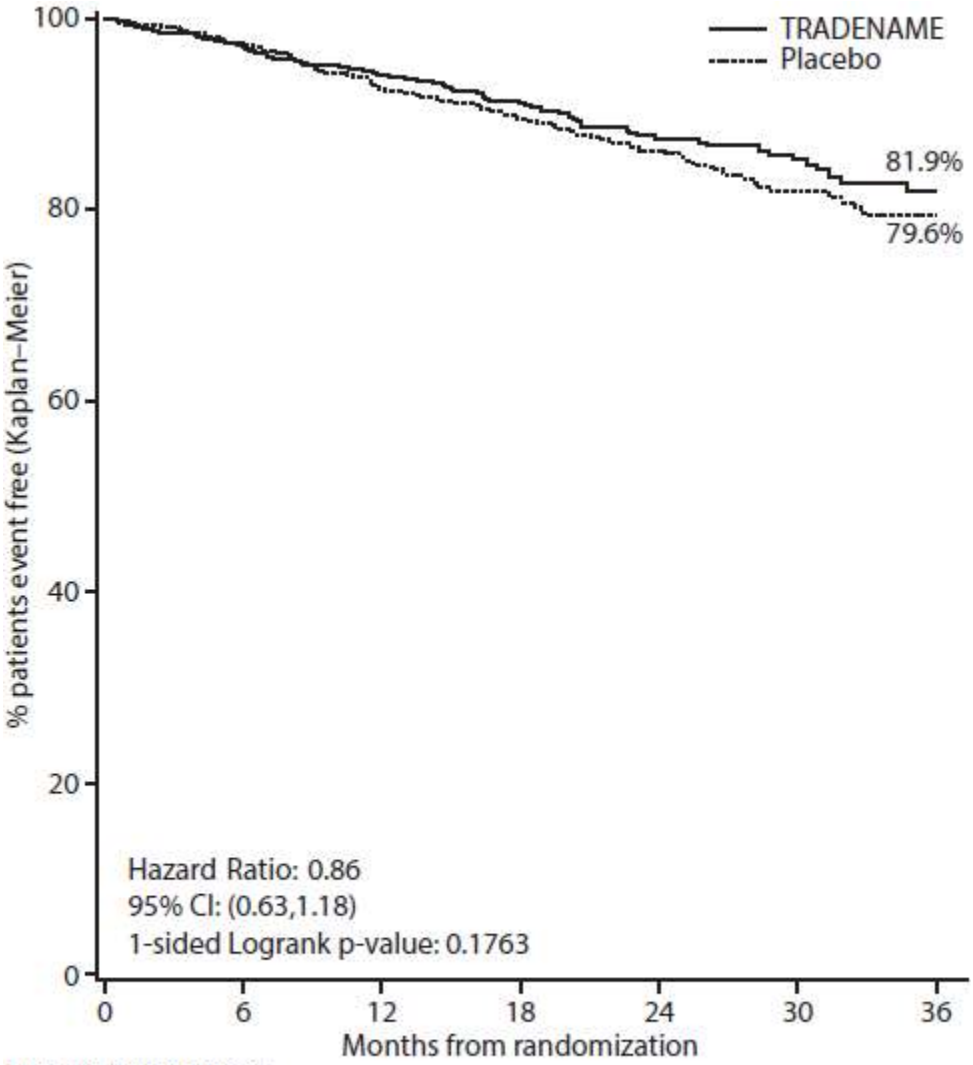
The total number of deaths of all causes up to study closure was 100 (17.4%) for the selexipag (Uptravi®) group and 105 (18.0%) for the placebo group (HR 0.97, 99% CI: 0.68, 1.39) (Figure 5).

Figure 5 Kaplan-Meier estimates of the occurrence of death up to study closure



The number of deaths due to PAH up to study closure was 70 (12.2%) for the selexipag (Uptravi®) group and 83 (14.3%) for the placebo group (Figure 6).

Figure 6 Kaplan-Meier estimates of the occurrence of death due to PAH up to study closure



Symptomatic endpoint

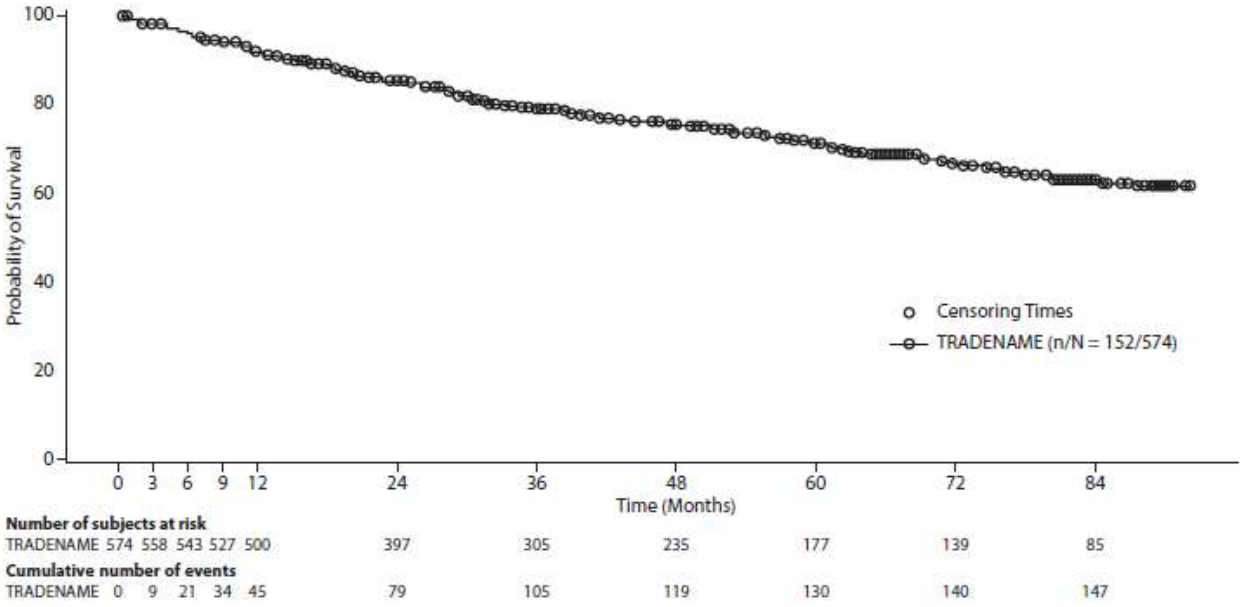
Exercise capacity was evaluated as a secondary endpoint. Treatment with selexipag (Uptravi®) resulted in a placebo-corrected median increase in 6MWD measured at trough (i.e., approximately 12 hours post-dose) of 12 meters at Week 26 (99% CI: 1, 24 meters, one-sided p value = 0.0027). In patients without concurrent PAH-specific therapy, the treatment effect measured at trough was 34 meters (99% CI: 10, 63 meters).

Long-Term Treatment of PAH

Patients enrolled into the pivotal study (GRIPHON) were eligible to enter a long-term open-label extension study. A total of 574 patients were treated with selexipag (Uptravi®) in the GRIPHON study; of these, 330 patients continued selexipag (Uptravi®) treatment in the open-label extension study. Kaplan-

Meier estimates of survival of these patients across the GRIPHON and the long-term extension study at 1, 2, 5 and 7 years were 92%, 85%, 71%, and 63%, respectively (Figure 7). The median follow-up duration was 4.5 years and the median exposure to selexipag (Uptravi®) was 3 years. Most patients were WHO FC II or III (47.6% and 51.2%, respectively); less than 1% of patients were in FC I (0.7%) or IV (0.5%) at baseline. The Kaplan-Meier estimates of survival at 1, 2, 5, and 7 years for patients of WHO FC I-II at baseline of the pivotal study were 97%, 91%, 81% and 70%, respectively, and for patients of WHO FC III-IV at baseline were 88%, 80%, 61% and 56%, respectively.

Figure 7 Kaplan-Meier estimates of time to death (all-causes) in long-term follow-up of selexipag (Uptravi®) treatment



Safety and Tolerability of selexipag (Uptravi®) Intravenous in Patients with PAH

The safety, tolerability and pharmacokinetics of selexipag (Uptravi®) intravenous in patients with stable PAH switching from an stable dose of selexipag (Uptravi®) tablets was demonstrated in a prospective, multicenter, open-label, single-sequence, cross-over, Phase 3 study, in 20 patients. Median age at baseline was 54 years (range: 40–75 years). At baseline all patients were receiving one or two PAH specific-therapies in addition to selexipag (Uptravi®).

The primary objective of the study was to assess whether temporary switching from a stable dose of selexipag (Uptravi®) tablets to a corresponding dose of selexipag (Uptravi®) intravenous and switching back to selexipag (Uptravi®) tablets was safe and well-tolerated in patients with stable PAH. A dose of selexipag (Uptravi®) intravenous that was 12.5% higher than the patient's usual oral dose was administered twice daily in order to keep the exposure to the active metabolite the same after oral and intravenous administration.

Enrolled patients had received selexipag (Uptravi®) tablets in the dose range of 400 to 1600 mcg twice a day and were switched to 3 infusions of selexipag (Uptravi®) intravenous. Subsequently, all patients switched to selexipag (Uptravi®) tablets without a change in tolerability, and completed the study.

Pharmacokinetic assessments were done pre- and post-switch and the results demonstrated comparable pharmacokinetic profile to the active metabolite between oral and intravenous administration.

No change in WHO FC or death were reported at any time during the study.

Pharmacokinetic Properties

The pharmacokinetics of selexipag and its active metabolite have been studied primarily in healthy subjects. The pharmacokinetics of selexipag and the active metabolite, both after single- and multiple-dose administration, were dose-proportional up to a single dose of 800 micrograms and multiple doses of up to 1800 micrograms twice a day. After multiple-dose administration, steady-state conditions of selexipag and active metabolite were reached within 3 days. No accumulation in plasma, either of parent compound or active metabolite, occurred after multiple-dose administration.

In healthy subjects, inter-subject variability in exposure (area under the curve over a dosing interval) at steady-state was 43% and 39% for selexipag and the active metabolite, respectively. Intra-subject variability in exposure was 24% and 19% for selexipag and the active metabolite, respectively.

With oral administration, exposure to selexipag and the active metabolite at steady-state in PAH patients and healthy subjects was similar. The pharmacokinetics of selexipag and the active metabolite in PAH patients were not influenced by the severity of the disease and did not change with time.

Absorption

Oral selexipag is rapidly absorbed and is hydrolyzed by carboxylesterases to its active metabolite.
Maximum observed plasma concentrations of selexipag and its active metabolite after oral administration are reached within 1–3 h and 3–4 h, respectively.

The absolute bioavailability of selexipag is approximately 49%.

In the presence of food, the exposure to selexipag after a single dose of 400 micrograms was increased by 10% in Caucasian subjects and decreased by 15% in Japanese subjects, whereas exposure to the active metabolite was decreased by 27% (Caucasian subjects) and 12% (Japanese subjects). More subjects reported adverse events after administration in the fasted than in the fed state.

Distribution

Selexipag and its active metabolite are highly bound to plasma proteins (approximately 99% in total, and to the same extent to albumin and alpha1-acid glycoprotein).

The volume of distribution of selexipag at steady state is 11.7 L.

Metabolism

Selexipag is hydrolyzed to its active metabolite in the liver and in the intestine by carboxylesterases. Oxidative metabolism catalyzed mainly by CYP2C8 and to a smaller extent by CYP3A4 leads to the formation of hydroxylated and dealkylated products. UGT1A3 and UGT2B7 are involved in the glucuronidation of the active metabolite. Except for the active metabolite, none of the circulating metabolites in human plasma exceeds 3% of the total drug-related material. Both in healthy subjects and PAH patients, after oral administration, exposure at steady-state to the active metabolite is approximately 3- to 4-fold higher than to the parent compound.

Excretion
Elimination of selexipag is predominantly via metabolism with a mean terminal half-life of 0.8–2.5 h. The active metabolite has a half-life of 6.2–13.5 h. The total body clearance of selexipag is 17.9 L/h. Excretion in healthy subjects was complete 5 days after administration and occurred primarily via feces (accounting for 93% of the administered dose) compared to 12% in urine.

Special populations
No clinically relevant effects of sex, race, age or body weight on the pharmacokinetics of selexipag and its active metabolite have been observed in healthy subjects or PAH patients.

Renal impairment
A 1.4- to 1.7-fold increase in exposure (maximum plasma concentration and area under the plasma concentration-time curve) to selexipag and its active metabolite was observed in subjects with severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73 m^2).

Hepatic impairment
In subjects with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, after a single dose administration of 400 micrograms of selexipag, exposure to selexipag was 2- and 4-fold higher, respectively, when compared to healthy subjects. Exposure to the active metabolite remained almost unchanged in subjects with mild hepatic impairment and was doubled in subjects with moderate hepatic impairment. Only two subjects with severe (Child-Pugh class C) hepatic impairment were dosed with selexipag. Exposure to selexipag and its active metabolite in these two subjects was similar to that in subjects with moderate (Child-Pugh class B) hepatic impairment.

Based on pharmacokinetic modeling of data from a study in subjects with hepatic impairment, exposure to the active metabolite at steady state in subjects with moderate hepatic impairment (Child-Pugh class B) after a once daily regimen is expected to be similar to that in healthy subjects receiving a twice daily regimen. The exposure to selexipag at steady state in subjects with moderate hepatic impairment during a once daily regimen is predicted to be approximately 2-fold that seen in healthy subjects receiving a twice daily regimen.

NON-CLINICAL SAFETY
Repeat-dose toxicity
In the repeated-dose toxicity studies in rodents, strong blood pressure decreases as a result of exaggerated pharmacology induced transient clinical signs and reduced food consumption and body-weight gain. In adult and juvenile dogs, intestine and bone/bone marrow were identified as the main target organs after treatment with selexipag. In dogs less than 1 year of age, intussusception due to prostacyclin-related effects on intestinal motility was observed sporadically. The effect occurred at 5-fold the human exposure (i.e., corrected for potency; 415-fold based on total exposure) (active metabolite). Safety margins based on no-observed-adverse-effect levels for the active metabolite, corrected for difference in receptor potency between human and dog, were 2-fold (i.e., corrected for potency; 180-fold based on total exposure) in relation to human exposure at a dose of 1600 micrograms of selexipag twice a day. The finding did not occur in mouse or rat toxicity studies. Because of the species-specific sensitivity of dogs to develop intussusception and the safety margin, this finding is considered not relevant for adult humans.

Increased bone ossification and related changes in the bone marrow in dog studies are considered to be due to the activation of EP_4 receptors in dogs. As human EP_4 receptors are not activated by selexipag or its active metabolite, this effect is species-specific and, therefore, not relevant to humans.

Carcinogenicity and Mutagenicity
Selexipag and the active metabolite are not genotoxic on the basis of the overall evidence of conducted genotoxicity studies.

In the 2-year carcinogenicity studies, selexipag caused an increased incidence of thyroid adenomas in mice and Leydig cell adenomas in rats. The mechanisms are rodent-specific. The findings were observed at exposures that were more than 25-fold above human exposure and are, therefore, not relevant for humans. Tortuosity of retinal arterioles was noted after 2 years of treatment only in rats. Mechanistically, the effect is considered to be induced by life-long vasodilation and subsequent changes in ocular hemodynamics. The finding is considered to be species-specific.

Reproductive Toxicology
Selexipag was not teratogenic in rats and rabbits, and had no effect on fertility of male and female rats. In the rat pre- and post-natal development study, selexipag induced no effects on maternal and pup reproductive function.

FertilitySelexipag had no effect on fertility of male and female rats.

THERAPEUTIC INDICATION
Selexipag (Uptravi®) is indicated for the long-term treatment of pulmonary arterial hypertension (PAH, WHO Group I) in adult patients with WHO functional class (FC) II–IV to delay disease progression. Disease progression included: death, hospitalization for PAH, initiation of intravenous or subcutaneous prostanoids, or other disease progression events (decrease of 6-minute walk distance [6MWD] associated with either worsened PAH symptoms or need for additional PAH-specific treatment).

Selexipag (Uptravi®) is effective in combination with an endothelin receptor antagonist (ERA) or a phosphodiesterase-5 (PDE-5) inhibitor, or in triple combination with an ERA and a PDE-5 inhibitor, or as monotherapy.

Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with congenital heart disease with repaired shunts [see ***Clinical Studies***].

DOSAGE AND METHOD OF ADMINISTRATION
Dosage

The recommended starting dose of Selexipag (Uptravi®) is 200 micrograms given twice daily, approximately 12 hours apart. The dose is increased in increments of 200 micrograms given twice daily, usually at weekly intervals, until adverse pharmacological effects that cannot be tolerated or medically managed are experienced, or until a maximum dose of 1600 micrograms twice daily is reached. During dose titration, it is recommended not to discontinue treatment in the event of expected pharmacological side effects since they are usually transient or manageable with symptomatic treatment [see ***Undesirable Effects***]. If a patient reaches a dose that cannot be tolerated, the dose should be reduced to the previous dose level.

Individualized dose titration
The goal is to reach the individually appropriate dose for each patient (the individualized maintenance dose).

Individualized maintenance dose
The highest tolerated dose reached during dose titration should be maintained. If the therapy over time is less tolerated at a given dose, symptomatic treatment or a dose reduction to the next lower dose should be considered.

Dosage modification guidelines
When co-administered with moderate CYP2C8 inhibitors (e.g., clopidogrel, deferasirox and teriflunomide), reduce the dosing of selexipag (Uptravi®) to once daily. Revert back to twice daily dosing frequency of selexipag (Uptravi®) when co-administration of moderate CYP2C8 inhibitor is stopped [see ***Interactions***].

Missed dose
If a dose of medication is missed, it should be taken as soon as possible. The missed dose should not be taken if it is almost time for the next scheduled dose (within approximately 6 hours).

If treatment is missed for 3 days or more, Selexipag (Uptravi®) should be re-started at a lower dose and then titrated.

Special populations
Pediatrics (< 17 years of age and younger)
The safety and efficacy of Selexipag (Uptravi®) in children have not been established.

Elderly (65 years of age and older)
No adjustment to the dosing regimen is needed in elderly patients.

Renal impairment
No adjustment to the dosing regimen is needed in patients with mild or moderate renal impairment.

No change in starting dose is required in patients with severe renal impairment. In patients with severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73 m^2) caution should be exercised during dose titration. There is no experience with selexipag (Uptravi®) in patients undergoing dialysis.

Hepatic impairment
No adjustment to the dosing regimen is needed in patients with mild hepatic impairment (Child-Pugh class A).

A once daily regimen is recommended in patients with moderate hepatic impairment (Child-Pugh class B) due to the increased exposure to and its active metabolite in this population. There is no clinical experience with selexipag (Uptravi®) in patients with severe hepatic impairment (Child-Pugh class C) (see ***Dosage and Method of Administration – Dose modification guidelines***).

Administration
The film-coated tablets are to be taken orally in the morning and in the evening.

Selexipag (Uptravi®) may be taken with or without food. Tolerability may be improved when taken with food.

The tablets should not be split, crushed or chewed, and are to be swallowed with some water.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

Concomitant use of strong inhibitors of CYP2C8 (e.g., gemfibrozil, [see ***Interactions***]).

WARNINGS AND PRECAUTIONS

Hyperthyroidism

Hyperthyroidism has been observed with Selexipag (Uptravi®) and other prostacyclin receptor agonists. Thyroid function tests are recommended as clinically indicated.

Pulmonary veno-occlusive disease

Should signs of pulmonary edema occur, consider the possibility of associated pulmonary veno-occlusive disease. If confirmed, discontinue Selexipag (Uptravi®).

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

Drug interaction studies have been performed in adult subjects using selexipag (Uptravi®) tablets. These results can be extrapolated to other routes of administration.

In vitro studies

Selexipag is hydrolyzed to its active metabolite by carboxylesterases [see ***Pharmacokinetic Properties***]. Selexipag and its active metabolite both undergo oxidative metabolism mainly by CYP2C8 and to a smaller extent by CYP3A4. The glucuronidation of the active metabolite is catalyzed by UGT1A3 and UGT2B7. Selexipag and its active metabolite are substrates of OATP1B1 and OATP1B3. Selexipag is a substrate of P-gp, and the active metabolite is a substrate of the transporter breast cancer resistance protein (BCRP).

Selexipag and its active metabolite do not inhibit or induce cytochrome P450 enzymes or transport proteins at clinically relevant concentrations.

In vivo studies

PAH-specific therapies: In the Phase 3 placebo-controlled study in patients with PAH, no relevant changes in the exposure (area under the plasma concentration-time curve during a dose interval) to selexipag and its active metabolite were observed when administered in combination with an ERA and/or PDE-5 inhibitor.

Anticoagulants or inhibitors of platelet aggregation: Selexipag is an inhibitor of platelet aggregation *in vitro*. In the Phase 3 placebo-controlled study in patients with PAH, no increased risk of bleeding was detected with selexipag compared to placebo, including when selexipag was administered with anticoagulants (such as heparin, coumarin-type anticoagulants) or inhibitors of platelet aggregation. In a study in healthy subjects, selexipag (400 micrograms twice a day) did not alter the exposure to S-warfarin (CYP2C9 substrate) or R-warfarin (CYP3A4 substrate) after a single dose of 20 mg warfarin. Selexipag did not influence the pharmacodynamic effect of warfarin on the international normalized ratio. The pharmacokinetics of selexipag and its active metabolite were not affected by warfarin.

Lopinavir/ritonavir: In the presence of 400/100 mg lopinavir/ritonavir, twice a day, a strong CYP3A4, OATP (OATP1B1 and OATP1B3) and P-gp inhibitor, exposure to selexipag increased approximately 2-fold, whereas the exposure to the active metabolite of selexipag did not change.

Gemfibrozil: In the presence of 600 mg gemfibrozil, twice a day, a strong inhibitor of CYP2C8, exposure to selexipag increased approximately 2-fold whereas exposure to the active metabolite increased approximately 11-fold. Concomitant administration of Selexipag (Uptravi®) with strong inhibitors of CYP2C8 (e.g., gemfibrozil) is contraindicated [see ***Contraindications***].

Clopidogrel: Concomitant administration of selexipag with clopidogrel (300 mg as a loading dose or maintenance dose of 75 mg once a day), a moderate inhibitor of CYP2C8, had no relevant effect on the exposure to selexipag and increased the exposure to the active metabolite by approximately 2.2-fold and 2.7-fold following loading dose and maintenance dose, respectively [see ***Dosage and Method of Administration - Dose Modification guidelines***].

Rifampicin: In the presence of 600 mg rifampicin, once a day, an inducer of CYP2C8 and UGT enzymes, the exposure to selexipag did not change whereas exposure to the active metabolite was reduced by half. Dose adjustment of selexipag (Uptravi®) may be required.

Midazolam: At steady state after up-titration to 1600 micrograms selexipag (Uptravi®) twice a day, no change in exposure to midazolam, a sensitive intestinal and hepatic CYP3A4 substrate, or its metabolite, 1-hydroxymidazolam, was observed. Concomitant administration of selexipag (Uptravi®) with CYP3A4 substrates does not require dose adjustment.

Inhibitors of UGT1A3 and UGT2B7: The effect of strong inhibitors of UGT1A3 and UGT2B7 on the exposure to selexipag or its active metabolite has not been studied. Concomitant administration of selexipag (Uptravi®) may result in a significant increase in exposure to selexipag or its active metabolite.

Hormonal contraceptives: Specific drug-drug interaction studies with hormonal contraceptives have not been conducted. Since selexipag did not affect the exposure to the CYP3A4 substrates midazolam and R-warfarin or the CYP2C9 substrate S-warfarin, reduced efficacy of hormonal contraceptives is not expected.

Pharmacodynamic interactions
Reductions in blood pressure may occur when Selexipag (Uptravi®) is administered with diuretics, antihypertensive agents, or other vasodilators.

PREGNANCY, BREAST-FEEDING AND FERTILITY
Pregnancy
There are limited data on the use of selexipag (Uptravi®) in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity [see ***Nonclinical Information***].

As a precautionary measure, it is preferable to avoid the use of Selexipag (Uptravi®) during pregnancy, unless clearly needed to do so.

Breast-feeding
It is unknown whether selexipag or its metabolites are excreted in human milk.

In rats, selexipag or its metabolites are excreted in the milk [for details see ***Nonclinical Information***].

Breastfeeding is not recommended during treatment with Selexipag (Uptravi®).

UNDESIRABLE EFFECTS
Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of selexipag based on the comprehensive assessment of the available adverse event information. A causal relationship with selexipag cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in theclinical trials of another drug and may not reflect the rates observed in clinical practice.

The most commonly reported adverse drug reactions related to the pharmacological effects of Selexipag (Uptravi®) are headache, diarrhea, nausea and vomiting, jaw pain, myalgia, pain in the extremity, flushing, and arthralgia. These reactions are more frequent during the dose titration phase. The majority of these reactions are of mild to moderate intensity.

The safety of selexipag (Uptravi®) oral treatment with film-coated tablets has been evaluated in a long-term, Phase 3, placebo-controlled study enrolling 1156 patients with symptomatic PAH. The mean treatment duration was 76.4 weeks (median 70.7 weeks) for patients receiving selexipag versus 71.2 weeks (median 63.7 weeks) for patients on placebo. The exposure to selexipag was up to 4.2 years.

Adverse reactions associated with selexipag over the entire treatment period in this study are presented in the table below. Frequency is reported according to CIOMS: very common $\geq$ 1/10, common $\geq$ 1/100 to < 1/10, uncommon $\geq$ 1/1000 to < 1/100, rare (≥ 1/10,000 to < 1/1000) and very rare (< 1/10,000).

Table 2 Adverse reactions[§]

	Double-blind PAH AC-065A302/GRIPHON		
System organ class	**Selexipag N = 575**	**Placebo N = 577**	**Frequency category**
Blood and lymphatic system disorders			
Anemia	8% (48)	5% (31)	Common
Nervous system disorders			
Headache*	65% (375)	32% (182)	Very common
Gastrointestinal disorders			
Diarrhea*	42% (244)	18% (106)	Very common
Nausea*	33% (192)	18% (105)	Very common
Vomiting*	18% (104)	9% (49)	Very common
Abdominal pain*	8% (48)	6% (33)	Common
Dyspepsia	4% (25)	2% (14)	Common
Metabolism and nutrition disorders			
Decreased appetite	6% (34)	3% (19)	Common
Musculoskeletal and connective tissue disorders			
Jaw pain*	26% (148)	6% (33)	Very common
Pain in extremity*	17% (97)	8% (44)	Very common
Myalgia*	16% (92)	6% (34)	Very common
Arthralgia*	11% (62)	8% (44)	Very common
Vascular disorders			
Flushing*	12% (70)	5% (28)	Very common
Hypotension	5% (29)	3% (18)	Common
Skin and subcutaneous tissue disorders			
Rash[1]	11% (64)	8% (48)	Very common
General disorders and administration site conditions			
Pain	3% (18)	1% (3)	Common
Endocrine disorders			
Hyperthyroidism	1% (8)	(0)	Common

[§] reported by 3% more in the active group vs placebo and/or if confirmed by laboratory findings (as appropriate) and/or if the adverse event is consistent with the pharmacology of the drug and hence a causal relationship was deemed at least as possible.

* see Section Description of selected adverse reactions.

[1]Based on the MedDRA high level group term of rash.

Description of selected adverse reactions

Pharmacological effects associated with titration and maintenance treatment

Adverse reactions associated with the pharmacological action of selexipag have been observed frequently, in particular during the phase of individualized dose titration. The placebo-corrected incidence during the titration and maintenance phase, respectively, were: headache (36 and 20%), diarrhea (24 and 16%), jaw pain (22 and 17%), nausea (16 and 10%), myalgia (10 and 6%), vomiting (10 and 2%), pain in extremity (9 and 7%), flushing (7 and 7%) and arthralgia (2 and 4%). These effects are usually transient or manageable with symptomatic treatment.

Table 3 Adverse reactions associated with pharmacological action of selexipag during titration and maintenance phase (> 3% placebo-corrected incidence in decreasing order)

	Selexipag	
Adverse reaction	**Titration phase (≤ 12 weeks) N = 509**	**Maintenance phase (> 12 weeks) N = 509**
Headache	36%	20%
Diarrhea	24%	16%
Jaw pain	22%	17%
Nausea	16%	10%
Myalgia	10%	6%
Vomiting	10%	2%
Pain in extremity	9%	7%
Flushing	7%	7%
Arthralgia	2%	4%

Laboratory abnormalities

Hemoglobin

In a Phase 3 placebo-controlled study in patients with PAH, mean absolute changes in hemoglobin at regular visits compared to baseline ranged from −0.34 to −0.02 g/dL in the selexipag group compared to −0.05 to 0.25 g/dL in the placebo group. A decrease from baseline in hemoglobin concentration to below 10 g/dL was reported in 8.6% of patients treated with selexipag and 5.0% of placebo-treated patients.

Thyroid function tests

In a Phase 3 placebo-controlled study in patients with PAH, a reduction (up to −0.3 MU/L from a baseline median of 2.5 MU/L) in median thyroid-stimulating hormone (TSH) was observed at most visits in the selexipag group. In the placebo group, little change in median values was apparent. There were no mean changes in triiodothyronine or thyroxine in either group.

Combination treatment of Selexipag (Uptravi®) with macitentan and tadalafil in newly diagnosed PAH patients

Safety of triple combination treatment (Selexipag (Uptravi®), macitentan and tadalafil) versus double combination (macitentan, tadalafil and placebo) in newly diagnosed PAH patients was evaluated in the double -blind, placebo-controlled TRITON clinical study. Treatment was initiated with macitentan 10 mg and tadalafil 20 mg (increased to 40 mg, if tolerated). Treatment with (Selexipag (Uptravi®) (N=119) or placebo (N=120) was initiated on Day 15 and patients were uptitrated per the current (Selexipag (Uptravi®) titration and dosing regimen (see ***Dosage and Method of Administration***). The median exposure was 90 weeks for patients receiving (Selexipag (Uptravi®) versus 78 weeks for patients on placebo.

While the safety and tolerability profile of (Selexipag (Uptravi®) was similar in both TRITON and GRIPHON studies, the frequencies for dyspepsia and anemia were higher in TRITON. Dyspepsia was reported in 16.8% of patients in the triple therapy group and 8.3% in the double therapy group, and anemia was reported in 13.4% of patients in the triple therapy group and 8.3% in the double therapy group.

The adverse reactions that occurred in at least 10% of patients in triple therapy group and ≥5% more commonly on (Selexipag (Uptravi®), macitentan and tadalafil than on placebo, macitentan, and tadalafil are shown in Table 4.

Table 4 Adverse Reactions Reported in at least 10% of patients and More Commonly (≥5%) on Selexipag (Uptravi®) + Macitentan + Tadalafil than on Placebo+Macitentan + Tadalafil in TRITON study

	Double-blind PAH AC-065A308/TRITON		
System organ class	**Selexipag (Uptravi®) + Macitentan + Tadalafil combination therapy N=119**	**Placebo + Macitentan + Tadalafil combination therapy N=120**	**Frequency category**
Nervous system disorders			
Headache	55.5% (66)	31.7% (38)	Very common
Gastrointestinal disorders			
Diarrhea	49.6% (59)	26.7% (32)	Very common
Nausea	41.2% (49)	21.7% (26)	Very common
Vomiting	24.4% (29)	10.8% (13)	Very common
Dyspepsia	16.8% (20)	8.3% (10)	Very Common
Musculoskeletal and connective tissue disorders			
Jaw pain	26.1% (31)	11.7% (14)	Very common
Pain in extremity	23.5% (28)	11.7% (14)	Very common
Vascular disorders			
Flushing	16.0% (19)	7.5% (9)	Very common
Blood and lymphatic system disorders			
Anemia	13.4% (16)	8.3% (10)	Very Common

Postmarketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience (Table 5). Because these reactions were

reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In the table, the frequencies are provided according to the following convention:

Very common ≥ 1/10 (≥ 10%)
Common ≥ 1/100 and < 1/10 (≥ 1% and < 10%)
Uncommon ≥ 1/1000 and < 1/100 (≥ 0.1% and < 1%)
Rare ≥ 1/10000 and < 1/1000 (≥0.01 and < 0.1%)
Very rare < 1/10000, including isolated reports (< 0.01%).
Not known Cannot be estimated from the available data

Table 5 Adverse reactions identified during postmarketing experience with selexipag (Uptravi®)

System Organ Class **Adverse Reaction**	**Frequency Category Calculated from Clinical Trials with selexipag (Uptravi®)**
Immune system disorders	
Hypersensitivity reactions	Common
Skin and subcutaneous tissue disorders	
Urticaria	Common
Angioedema	Common

OVERDOSE
Isolated cases of overdose with selexipag (Uptravi®) tablets up to 3200 mcg were reported.

Symptoms and signs
Mild, transient nausea was the only reported consequence.

Treatment
In the event of overdose, supportive measures must be taken as required. Dialysis is unlikely to be effective because and its active metabolite are highly protein-bound.

STORAGE CONDITIONS
Store at temperatures not exceeding 30°C. Keep out of reach and sight of children. No special requirements for disposal.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Patient must seek medical attention immediately at the first sign of any adverse drug reaction. For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.

Questions or comments? Email us at Janssendrugsafety_Phil@its.jnj.com.

AVAILABILITY
Alu/alu blister pack x 10/Box of 60's
Alu/alu blister pack x 10/Box of 140's (Selexipag (Uptravi®) 200 mcg titration pack only)

REGISTRATION NUMBER

200 mcg: DR-XY47389
400 mcg: DR-XY47390
600 mcg: DR-XY47391
800 mcg: DR-XY47392
1000 mcg: DR-XY47393
1200 mcg: DR-XY47394
1400 mcg: DR-XY47395
1600 mcg: DR-XY47396

DATE OF FIRST AUTHORIZATION
200 mcg: 20 SEP 2021
400 mcg: 20 SEP 2021
600 mcg: 20 SEP 2021
800 mcg: 20 SEP 2021
1000 mcg: 20 SEP 2021
1200 mcg: 20 SEP 2021
1400 mcg: 20 SEP 2021
1600 mcg: 20 SEP 2021

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